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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 04/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/044,716	LANGENFELD, JOHN	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 November 2004 and 13 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6,9,11,12,14-25,27,29 and 31-64* is/are pending in the application.

4a) Of the above claim(s) *3,4,11,12,20-25,27,29 and 31-64* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,6,9 and 14-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 May 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *20020625;20020705*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *IDS:20020812*.

DETAILED ACTION

1. The election with traverse filed November 17, 2004 is acknowledged and has been entered.

Applicant has elected the invention of Group I, claims 2 and 5-10, drawn to a method for treatment of cancer comprising administering to a patient a therapeutically effective amount of a polypeptide that binds specifically to bone morphogenetic protein-2 (BMP-2).

2. The supplemental election with traverse filed January 13, 2005 is acknowledged and has been entered.

Applicant has elected the species of the invention of Group I, wherein said noggin is human noggin (i.e., the polypeptide of SEQ ID NO: 4).

3. The amendment filed November 17, 2004 is acknowledged and has been entered. Claims 5, 7, 8, 10, 13, 26, 28, and 30 have been canceled. Claim 12 has been amended.

4. The amendment filed January 13, 2005 is acknowledged and has been entered. Claims 6 and 9 have been amended.

5. Claims 1-4, 6, 9, 11, 12, 14-25, 27, 29, and 31-64 are pending in the application. Claims 3, 4, 11, 12, 20-25, 27, 29, and 31-64 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on November 17, 2004.

6. Claims 1, 2, 6, 9, and 14-19 are currently under prosecution.

Election/Restrictions

7. In the paper filed November 17, 2004, Applicant traversed the restriction and election requirement set forth in the Office action mailed October 20, 2004.

Applicant's arguments have been carefully considered but have not been found persuasive for the following reasons:

Applicant has argued that the inventions of Groups I and III are not properly restricted, since the inventions of Group I are methods comprising administering an inhibitor of BMP-2 that is a polypeptide, whereas the inventions of Group III are methods comprising administering an inhibitor of BMP-2 that is an antibody, and an antibody is a polypeptide. The inventions of Groups I and III are patentably distinct inventions for the reasons set forth in the Office action mailed October 20, 2004. Although an antibody can be composed of a single-chain, as stated in the Office action, it is generally not. Nonetheless, the structure and function of an antibody is highly distinctive; so, as the artisan of ordinary skill in the art would readily appreciate, even if an antibody were composed of a single polypeptide, it is readily distinguishable from a polypeptide that is not an antibody. In addition, the search required to examine claims directed to the inventions of Group I is not the same, nor is it coextensive with that required to examine claims drawn to the invention of Group III. This fact is made evident, for example, by their different classifications. Because the searches are not the same, a different search would have to performed to examine claims directed to either invention. The need to perform more than one search would constitute a serious burden. Because the inventions are patentably distinct and because both inventions cannot be searched and examined without serious burden, restriction of the inventions is proper.

In the paper filed January 13, 2005, Applicant further traversed the restriction and election requirement set forth in the Office action mailed October 20, 2004.

Applicant's arguments have been carefully considered but have not been found persuasive for the following reasons:

By the paper filed January 13, 2005, Applicant has amended the claims of the elected invention such that those claims are not specifically drawn to any species of invention other than the elected species of invention. Applicant's arguments are therefore moot.

Accordingly, the restriction and election requirement set forth in the Office action mailed October 20, 2004 is deemed proper and therefore made FINAL.

Information Disclosure Statement

8. The information disclosures filed June 21, 2002, June 28, 2002, and August 6, 2002 have been considered. An initialed copy of each is enclosed.

Priority

9. Applicant's claim to the benefit of the earlier filing dates of U.S. Provisional Application Nos. 60/261,252 filed January 12, 2001 is acknowledged.

However, with respect to claims 9 and 15, it is noted that Applicant has not complied with one or more conditions for receiving the benefit of the earlier filing dates of the provisional application under 35 U.S.C. § 119(e) for the following reason:

U.S. Provisional Application No. 60/261,252 does not disclose the claimed invention in a manner that would satisfy the requirements set forth under 35 U.S.C. § 112, first paragraph. In particular, the provisional application does teach or fairly suggest treating cancer by administering a BMP-2 inhibitor that is a polypeptide comprising a fragment (i.e., at least 10 consecutive amino acids) of noggin. Furthermore, it is noted that the provisional application fails to disclose that the claimed invention can be used to treat endometrial cancer, omental cancer, testicular cancer, or liver cancer, as recited in claim 15 of the present application.

To receive benefit of the earlier filing date under 35 USC § 119(e), the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional

application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. § 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

Accordingly, the effective filing date of the instant claims 9 and 15 is considered to be this present application was filed, namely January 11, 2002.

Response to Amendment

10. The amendment filed June 25, 2002 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

These separated RT-PCR products were not sequenced, however, and the "BMP-2 primers" used were potentially capable of amplifying both BMP-2 and BMP-4, which are highly homologous. Thus, this data alone cannot be definitively interpreted as showing amplification of BMP-2 in the absence of sequencing data

Applicant has submitted that the amendment clarifies "conclusions that could have been drawn from the RT-PCR data that was available at the time the application was filed and to comply with the duty of disclosure under 37 C.F.R. 1.56" (Paper filed June 25, 2002, page 2, paragraph 2). Applicant has further submitted that "[b]ecause the amendment simply clarifies rather than augments the data, it does not constitute new matter".

Applicant has suggested that the conclusion could have been drawn from the RT-PCR data shown in Figure 2; however, the disclosure does not reveal the fact that primers that were used to amplify nucleic acid encoding BMP-2 were not specific. Moreover, the disclosure does not suggest that any such conclusion could have been drawn from the data.

Applicant is required to cancel the new matter in the reply to this Office Action.

Specification

11. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required:

Originally claim 9 recited, "wherein the bone morphogenetic-2 activity inhibitor is a polypeptide the amino acid sequence of which comprises at least ten consecutive amino acids of noggin". This claim language finds no antecedent basis in the originally filed supporting disclosure.

12. The specification is objected to because the use of numerous improperly demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

Examples of such improperly demarcated trademarks include GenBank™ (page 17, line 16), Pharmacia™ (page 37, line 8), ABI Prism™ (page 37, lines 14 and 15), and Tween™ (page 41, line 21).

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at http://www.uspto.gov/web/menu/search.html.

13. The specification is objected to because of the following informalities:

(a) The misspelling of "ABI Prism™" as "IBI Prism™" at page 37, lines 14 and 15.

(b) The mistyping of "4°C" as "4oC" at page 39, line 3.

Claim Objections

14. Claim 18 is objected to for the following reason:

Claim 18 is drawn to the method of claim 1, wherein the "bone morphogenetic protein-2 activity inhibitior" further comprises a pharmaceutically acceptable carrier. The specification discloses that the "bone morphogenetic protein-2 activity inhibitior" is, for example, "human noggin of SEQ ID NO: 4", as recited in claim 6. Human noggin is a protein; it does not "further comprise a pharmaceutically acceptable carrier". Similarly, other "bone morphogenetic protein-2 activity inhibitior" are compounds that do not further comprise a pharmaceutically acceptable carrier. On the other hand, a composition may comprise "bone morphogenetic protein-2 activity inhibitior" and still further comprise a pharmaceutically acceptable carrier. Appropriate rebuttal or correction is required.

15. Claim 19 is objected to because of the inadvertent typographical omission of a comma after "intraveneously". Appropriate correction is required.

Claim Rejections - 35 USC § 112

16. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

17. Claims 1, 2, 9, and 14-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the

inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "written description" rejection.

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, "Written Description" Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

The claims are drawn to a method for the treatment of cancer comprising administering to a patient a therapeutically effective amount of a "BMP-2 activity inhibitor".

At page 4, paragraph [0011], through page 5, paragraph [0012], for example, the specification describes the "BMP-2 activity inhibitor" as a polypeptide that binds BMP-2, a polypeptide that binds a receptor of BMP-2, an antibody that binds specifically to BMP-2, an antisense oligonucleotide that inhibits the expression of a nucleic acid encoding BMP-2, a known antagonist of BMP-2, such as noggin, chordin, Cerberus 1 homolog, gremlin, and DAN, and a fragment of such known antagonists.

The structural and functional variability of the members of the genus of agents that are capable of inhibiting an activity of BMP-2 is evident upon consideration of the disparate structures and functions of the various different types of molecules or compounds that are used in practicing the invention (e.g., an antisense oligonucleotide vs. an antibody vs. a ligand of BMP-2). This variability is further evident upon consideration of the disparate structures and functions of the known, naturally occurring inhibitors of an activity of BMP-2 (e.g., noggin, gremlin, etc.), which are described as useable in practicing the invention.

Consequently, given the broadest reasonable interpretation, the claims are directed to a genus of agents (i.e., "BMP-2 activity inhibitors") that differ both

structurally and functionally, despite having the common ability to reduce an apparent activity of the BMP-2 in a patient treated using the claimed invention.

Notably, the specific activity of BMP-2 that is inhibited by the members of this genus of agents is not described. It follows therefore that claims are directed to a genus of agent capable of inhibiting any apparent activity of BMP-2 that is measurable or determinable by any number of assays that describe any one of its many biologic functions (e.g., the ability to bind a receptor of BMP-2; the ability to bind noggin; the ability of BMP-2 to stimulate the growth of tumors; or the ability of BMP-2 inhibit the growth of tumors).

However, apart from known naturally occurring inhibitors of BMP-2 (e.g., noggin), the specification does not adequately describe the members of the genus of agents capable of inhibiting an activity of BMP-2, such that the skilled artisan could immediately envision, recognize, or distinguish at least a substantial number.

Moreover, as disparate are the chemical structures and functions of the various different types of agents, the prior art teaching such agents, then, constitutes factual evidence that the skilled artisan could not immediately reasonably conclude that Applicant had possession of the claimed invention at the time the application was filed, because the specification necessarily fails to describe any particularly identifying (i.e., substantial) *structural* feature that is commonly shared by the agents capable of inhibiting an activity of BMP-2, which might permit the skilled artisan to envision, recognize, or distinguish these and other members of the genus of agents to which the claims are directed. For example, an antibody and an antisense oligonucleotide share no substantial structural feature, if any at all, that correlates with their ability to inhibit an activity of BMP-2. Neither the antibody nor the antisense oligonucleotide share a substantial structural feature with the few adequately described agents (e.g., noggin) that are capable of inhibiting an activity of BMP-2 and which are therefore useable in practicing the invention; and as a final example, an antibody that binds a receptor of BMP-2 and an antibody that binds BMP-2, although both

are perhaps capable of inhibiting the ability of BMP-2 to bind the receptor, share no common particularly identifying structural feature that is essential to that capability, since the antibodies comprise functionally distinct antigen-binding domains.

With further regard to those agents that are adequately described, namely the naturally occurring inhibitors of an BMP-2 activity (Noggin, Chordin, Cerberus 1 homolog, Gremlin, and DAN), again, as the structures and functions of these ligands of BMP-2 vary considerably, there is no disclosed or known structural feature, which is particularly identifying of those proteins or that is shared by at least most of those proteins, that correlates with their common ability to inhibit an activity of BMP-2. Accordingly, these proteins are not representative of each other, nor of the genus of agents to which the claims are directed, which have the ability to inhibit an activity of BMP-2 to achieve therapeutic effect in treating cancer.

Furthermore, the Federal Circuit has decided that a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. See *Noelle v. Lederman*, 69 USPQ2d 1508 1514 (CA FC 2004) (citing *Enzo Biochem II*, 323 F.3d at 965; *Regents*, 119 F.3d at 1568). As discussed in greater detail below in the rejection of claims as lacking an enabling disclosure, there is in fact such unpredictability.

As the claims encompass the use of fragments of these naturally occurring proteins to treat cancer, it is duly noted that the supporting disclosure does not describe which fragments comprising at least ten consecutive amino acids of noggin, or any of the other proteins, are capable of inhibiting an activity of BMP-2. "[G]eneralized language may not suffice if it does not convey the detailed identity of an invention." *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004). In this instance, as in that, there is no language that adequately describes fragments of the known inhibitors of a BMP-

2 activity that can be used to achieve the claimed therapeutic effect. A description of what a material does, rather than of what it is, does not suffice to describe the claimed invention.

While the written description requirement can by satisfied without an actual reduction to practice, the disclosure of a catalog of potentially effective substances that might be found to be useful in practicing the claimed invention does not fulfill the written description requirement. Recognizing that the claims are drawn to a method comprising administering to a patient an unspecified substance having the ability to inhibit an activity of BMP-2, it is aptly noted that the Federal Circuit has decided that a generic statement that defines a genus of substances by *only* their functional activity, i.e., the ability to inhibit an activity of BMP-2 to achieve therapeutic effect, does not provide an adequate written description of the genus. See *The Reagents of the University of California v. Eli Lilly*, 43 USPQ2d 1398 (CAFC 1997). The Court indicated that while applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a precise definition of a representative number of members of the genus, such as by reciting the structure, formula, chemical name, or physical properties of those members, rather than by merely reciting a wish for, or even a plan for obtaining a genus of molecules having a particular functional property. The recitation of a functional property alone, which must be shared by the members of the genus, is merely descriptive of what the members of genus must be capable of doing, not of the substance and structure of the members.

Although *Lilly* related to claims drawn to genetic material, the statute applies to all types of inventions. "Regardless whether a compound is claimed *per se* or a method is claimed that entails the use of the compound, the inventor cannot lay claim to the subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods". *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1984 (CAFC 2004). The

claimed method depends upon finding a compound that has the ability to inhibit an activity of BMP-2 to achieve therapeutic effect in treating cancer using the claimed process; without such a compound, it is impossible to practice the invention.

In addition, although the skilled artisan could potentially identify agents that might be used in practicing the claimed invention by screening for substances that are capable of inhibiting an activity of BMP-2 to achieve therapeutic effect in treating cancer, it is duly noted that the written description provision of 35 U.S.C § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it.

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed*.

Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (CAFC 1991). See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993); *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016 (CAFC 1991); *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

Absent the adequate description of a representative number of members of the genus of agents to which the claims are directed, the supporting disclosure amounts to no more than a mere invitation to identify a substance that can be used as an agent for treating cancer by inhibition of an activity of BMP-2.

Finally, Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description'' Requirement (66 FR 1099-1111, January 5, 2001) states, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was

in possession of the claimed invention" (*Id.* at 1104). Moreover, because the claims encompass a genus of substances having the ability to inhibit an activity of BMP-2 to achieve therapeutic effect in the treatment of cancer, which vary both structurally and functionally, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. In this instance, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; Applicant has not shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; and Applicant has not described distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention at the time the application was filed.

Notably the Federal Circuit has recently decided that the description of a fully characterized molecular target of an antibody is sufficient to adequately describe an antibody that binds that target. See *Noelle v. Lederman*, 69 USPQ2d 1508 (CA FC 2004). However, the same court decided that each case involving the issue of written description, "must be decided on its own facts. Thus, the precedential value of cases in this area is extremely limited." *Vas-Cath*, 935 F.2d at 1562 (quoting *In re Driscoll*, 562 F.2d 1245, 1250 (C.C.P.A. 1977)). In that instance, the claims are drawn to an antibody that inhibits an activity of BMP-2. BMP-2, for example, is a fully characterized antigen; were the claims directed to an antibody that binds BMP-2, the written description would be met by the description of the fully characterized antigen alone. However, in this instance, the claims are not directed to an antibody that merely binds its molecular target, but rather to an antibody that binds to its molecular target and thereby inhibits an activity of BMP-2 to produce a therapeutic effect in a patient diagnosed with cancer. While the particular activity of BMP-2 that is inhibited is not specified in the claims, nor limited by the supporting disclosure, an antibody

that binds BMP-2 is not reasonably expected to inhibit an activity of BMP-2, since some antibodies are expected to bind without consequence, while others are expected to bind and either stimulate or inhibit that activity. Moreover, some antibodies that bind BMP-2 are expected to inhibit the growth of cancer cells, while others are expected to have either no effect or to actually promote their growth. This assertion is supported, for example, by the teachings of Stancoviski et al. *(Proceedings of the National Academy of Science USA.* 1991; **88**: 8691-8695). Stancovski et al. characterizes the effects upon the growth of tumor cells of various different antibodies that each bind the extracellular domain of a tumor-associated antigen, ErbB2; see entire document (e.g., the abstract). Stancovski et al. teaches some anti-ErbB2 antibodies inhibited tumor cell growth, but others actually accelerated their growth (page 8693, column 1). Furthermore, as explained below in the rejection of the claims as lacking an enabling disclosure, the role of BMP-2 in cancer cells varies, such that the inhibition of its activity can either inhibit or promote the growth of cancer in a patient. Accordingly, the mere generalized description of antibodies that bind and inhibit an activity of BMP-2, although a fully characterized antigen, cannot suffice to describe antibodies that have a therapeutic effect, because the skilled artisan could not immediately envision, recognize, or distinguish antibodies that bind BMP-2 to inhibit an activity thereof, which have therapeutic effect (e.g., inhibit the growth of cancer cells), from such antibodies that lack therapeutic effect (e.g., promote the growth of cancer cells). Here, the specification does not exemplify the use of an antibody that binds to BMP-2 and thereby inhibits an activity of the protein to produce a therapeutic effect in a subject diagnosed with cancer, nor is there reference to a deposit of such an antibody or a description of its chemical structure, so there is no factual evidence suggesting that Applicant had possession of such an antibody capable of inhibiting an activity of BMP-2 and thereby causing a therapeutic effect at the time the application was filed. It should be noted that the foregoing discussion is intended to be exemplary, as the claims are not limited to a method comprising administering an antibody that

binds BMP-2. It stands to reason that not all of the molecular targets of a therapeutic antibody, which might be useful in practicing the claimed process, have been identified and fully characterized.

18. Claims 1, 2, 6, 9, and 14-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The amount of guidance, direction, and exemplification set forth in the supporting disclosure is not reasonably commensurate in scope with the claims, nor is it sufficient to enable the skilled artisan to practice the claimed process without undue experimentation.

Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). These factors include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

First of all, the presumed utility of the claimed invention is largely based upon a disclosure in the specification of an observation that BMP-2 is overexpressed in lung cancer cells, as compared to normal lung cells; see, e.g., page 4, paragraph [0009]. However, by the amendment filed June 25, 2002, Applicant sought to amend the specification to indicate that because the primers used to amplify the nucleic acids encoding BMP-2 were potentially capable of amplifying both BMP-2 and BMP-4, which are highly homologous, the data presented therein cannot be definitively interpreted as showing amplification of BMP-2 in the absence of sequencing data. Then, at page 2 of that amendment,

Applicant has remarked that subsequent sequencing of the RT-PCR products revealed amplification of BMP-4 rather than BMP-2. Since it seems that the underlying premise upon which the utility of claimed invention is asserted is amiss, it is questionable whether the pharmacologic inhibition of BMP-2 should be expected to produce a therapeutic effect in treating cancer.

Nonetheless, as explained above in the rejection of the claims as lacking a sufficient description in the supporting disclosure, the claims are directed to a genus of structurally and functionally different molecules or compounds that inhibit an activity of BMP-2. However, proteins, such as BMP-2, are multifunctional, and the specific activity that is inhibited by the members of the genus of molecules and compounds to which the claims are directed is not specified, nor is it described in a limiting manner elsewhere in the specification. The molecules and compounds include such highly disparate molecules as antibodies and antisense oligonucleotides; yet, the only members of the genus that are adequately described are a few naturally occurring proteins that are known inhibitors of an activity of BMP-2, such as noggin. However, apart from the procurement of noggin from a commercial source, the production of molecules and compounds that are used in practicing the claimed invention is not exemplified.

The claims specifically encompass the use of fragments of human noggin that comprise at least 10 consecutive amino acids of its amino acid sequence (i.e., SEQ ID NO: 4). However, the specification does not teach which fragments of noggin are capable of inhibiting an activity of BMP-2, nor does it describe which portions of the amino acid sequence are essential to the ability of the protein to inhibit any particular activity of BMP-2.

The claims are drawn to a method for treating cancer in a patient; however, the use of claimed invention to treat cancer in a patient is not exemplified in the specification. The specification only shows that subcutaneous *co-injection* of agarose beads coated with recombinant mouse noggin and A549 lung cancer cells reduced the growth of the resulting tumor in nude mice; see,

e.g., Figure 14; page 10, paragraph [0031]; and pages 40 and 41, paragraph [0102] (Example 5). Therefore, as the claimed invention cannot be practiced in the "real world" by co-injecting the "BMP-2 activity inhibitor" together with the tumor cells to be treated in a patient, the claimed invention has not been exemplified. Moreover, the claimed invention has not been shown to produce a therapeutic effect in a patient diagnosed with an established tumor.

Although most of the claims are not specifically limited to any one type of cancer, the specification discloses that in particular the invention is used to treat lung cancer, bladder cancer, breast cancer, colon cancer, kidney cancer, ovarian cancer, thyroid cancer, endometrial cancer, omental cancer, testicular cancer, and liver cancer; see, e.g., page 4, paragraph [0010]. The specification, however, only shows that noggin can reduce the growth of lung cancer cells injected subcutaneously in nude mice.

Much of that disclosed in the present application has been published. Langenfeld et al. (*Carcinogenesis*. 2003; **24** (9): 1445-1454) teaches that BMP-2, but not BMP-4 is overexpressed in non-small cell lung cancer cells, as compared to normal lung cells or benign tumor cells of the lung; see entire document (e.g., the abstract). Langenfeld et al. shows that ectopic, enforced expression of BMP-2 in a A549 lung cancer cell line enhanced the growth of tumors in nude mice inoculated with these cells; see, e.g., the abstract. Langefeld et al. teaches inhibition of BMP-2 activity by recombinant noggin or an antibody that binds BMP-2 significantly reduced this tumor growth; see, e.g., the abstract. However, as in the disclosed examples, the inhibitors were *co-injected* with the A549 lung cancer cells (page 1447, column 1). Langenfeld et al. concludes that these data demonstrate that BMP-2 *may* have important biological activity in human lung carcinomas but cautions that "[f]urther studies are needed to define the specific mechanisms activated by BMP-2 in human carcinomas" (page 1453, column 1).

Notwithstanding, Applicant is reminded that supporting documents cannot be relied upon to correct the deficiencies of the specification by supplying the

necessary and essential teachings, guidance, and exemplification that the specification lacks. See MPEP § 2164.05(a).

More recently Langenfeld and colleagues have published an additional report (Langenfeld et al., *Molecular Cancer Research.* 2004 Mar; 2: 141-149) that discloses although BMP-2 is highly overexpressed in the majority of patient-derived lung carcinomas, a mechanism revealing its role in cancer has not been established; see entire document (e.g., the abstract). Similarly, Langenfeld et al. disclose that the role of BMP family members in vascular development has not been extensively studied (e.g., page 145, column 1); however, Langenfeld et al. discloses results that they conclude show that inhibition of BMP-2 by noggin or antisense transfection decreases the lung tumor vasculature in their nude mouse model (e.g., page 145, column 2). Thusly, Langenfeld et al. discloses a study that furthers our understanding of the role of BMP-2 in lung cancer; it is however apparent that our understanding is not yet complete (e.g., page 146, column 2, through page 147, column 1). In particular, Langenfeld et al. discloses that while the inhibition of BMP-2 activity by noggin in A549 lung cancer cells appears to inhibit the growth of the tumor in nude mice, other studies have demonstrated quite paradoxically that the inhibition of BMP-2 activity in different types of tumor cells may actually promote their growth (page 147, column 1).

Indeed, Tada et al. (*Oncol. Rep.* 1998 Sep-Oct; **5** (5): 1137-1140), for example, have reported that treatment of the same A549 lung cancer cells used by Langenfeld and colleagues in their studies with BMP-2 resulted in *inhibition* of their growth in anchorage-dependent and independent growth conditions; see entire document (e.g., the abstract). Accordingly, the skilled artisan might reasonably conclude that inhibiting the activity of BMP-2 by, for example, exposing tumor cells to noggin would not be therapeutic, since it would to the contrary be expected that inhibiting BMP-2 might actually promote the growth of the tumor.

Just how the opposing conclusions of Langenfeld et al. and Tada et al. might be reconciled is not known, but the need to further clarify the role of BMP-2 in tumorigenesis before practicing the claimed invention is apparent.

Still others have reported that BMP-2 has an inhibitory role, rather than a stimulating role, in lung carcinogenesis. For example, Buckley et al. (*Am. J. Physiol. Lung Cell Mol. Physiol.* 2004; **286**: L81-L86) have disclosed results that they conclude show that BMP-2 suppresses the transformed phenotype of A549 cells in vitro; see entire document (e.g., the abstract). Similarly, Buckley et al. reports that BMP-4 can induce senescence and thus negatively regulate the growth of A549 lung cancer cells (e.g., abstract). Again, the results published by Buckley et al. would suggest that contrary to the assertions set forth in the instant application, the inhibition of BMP-2 would not be therapeutic.

While Langenfeld and colleagues have concluded that BMP-2 promotes angiogenesis, since, e.g., its inhibition diminished blood vessel formation (Langenfeld et al. 2004, *supra*; e.g., abstract), and therefore promotes tumorigenesis, other investigators have posed that BMP-2 has a role in preventing cancer. Hardwick et al. (*Gastroenterology*. 2004 Jan; **126** (1): 111-121), for example, concludes that BMP-2 acts as a tumor suppressor, since their study shows the protein promotes apoptosis and differentiation and inhibits proliferation of mature colonic epithelial cells; see entire document (e.g., the abstract). In fact, Hardwick et al. discloses that expression of the gene encoding BMP-2 in dysplastic epithelial cells of microadenomas acquired from patients genetically predisposed to colorectal cancer is lost (page 118). Contrary to the presumed utility of administering to a patient diagnosed with cancer an inhibitor of BMP-2 activity, which asserted in this application, Hardwick et al. discloses that administering noggin to mice led to reduced apoptosis of colon cells; see, e.g., page 117, Figure 7. Hardwick et al. concludes, as loss of BMP signaling appears to lead to decreased apoptosis, its loss would be expected to be associated with increased carcinogenesis (page 120). Similarly, Haramis et al. (*Science*. 2004 Mar 12; **303**: 1684-1686) published the results of a study that

they conclude shows that loss of BMP-4 activity leads to colon polyp growth and ultimately neoplasia (i.e., cancer); see entire document (e.g., the abstract). Haramis et al. discloses that inhibiting BMP signaling by noggin results in the formation of cellular structures in the colonic crypts, which mirror those that occur in patients predisposed to cancer by the syndrome juvenile polyposis (e.g., abstract). More recently, Nishanian et al. (Biochem. Biophys. Res. Com. 2004; 323: 91-97) teaches that inactivation of BMP signaling by mutation of a BMP receptor actually causes familial juvenile polyposis; see entire document (e.g., the abstract).

In other types of cancer, too, including, for example, breast cancer cells, BMP-2 has been reported to act as an antiproliferative agent. For example, Ghosh-Choudhury et al. (*Biochem. Biophys. Res. Com.* 2000; **272**; 705-711) discloses that BMP-2 dose-dependently inhibits the growth of MDA MB 231 human breast cancer cells; see entire document (e.g., the abstract). By way of mechanism, Ghosh-Choudhury et al. discloses that BMP-2 treatment arrests the cells in the G1 phase of the cell cycle, perhaps as a result of causing the hypophosphorylation of the retinoblastoma protein (Rb) and increasing the expression of the tumor suppressor p21 (e.g., abstract). Apparently, BMP-2 also causes hypophosphorylation of Rb and increases expression of p21 in prostate cancer cells, which Tomari et al. (*Int. J. Mol. Med.* 2005 Feb; **15** (2): 253-258) teaches may explain how BMP-2 inhibits their proliferation; see entire document (e.g., the abstract). Still others (e.g., Nakamura et al. (*Biochem. Biophys. Res. Com.* 2003; **307**: 206-213) and Wen et al. (*Biochem. Biophys. Res. Com.* 2004; **316**: 100-106)) have shown that BMP-2 acts to suppress the growth of gastric and brain cancer cells.

Accordingly, given that the role of BMP-2 in cancer has not yet been fully characterized, and contrary to the implications of the data disclosed in the instant application, most reports suggest that its role is to inhibit tumorigenesis, the skilled artisan could not use the claimed invention without undue

experimentation. It is not clear that the inhibiting an activity of BMP-2 should be reasonably expected to be therapeutic in the treatment of cancer.

Furthermore, one cannot extrapolate the teachings of the specification to the enablement of the invention, particularly in the absence of exemplification that is commensurate in scope with the claims, because it is well known that the art of drug discovery for is highly unpredictable. With particular regard to anticancer drug discovery, Gura (*Science.* 1997; **278**: 1041-1042), for example, teaches that researchers are faced with the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile (abstract). Because of a lack of predictability, Gura discloses that often researchers merely succeed in developing a therapeutic agent that is useful for treating the animal or cell that has been used as a model, but which is ineffective in humans, and indicates that the results acquired during pre-clinical studies are often non-correlative with the results acquired during clinical trials (page 1041, column 2). Gura very succinctly teaches our lack in ability to reliably extrapolate pre-clinical data to accurately predict the outcomes of such treatments in humans is due to the fact that "xenograft tumors don't behave like naturally occurring tumors in humans" (page 1041, column 2). Gura teaches that although researchers had hoped that xenografts would prove to better models for studying cancer in humans and screening candidate therapeutic agents for use in treating patient diagnosed with cancer, "the results of xenograft screening turned out to be not much better than those obtained with the original models". Gura states that as a result of their efforts, " '[w]e had basically discovered compounds that were good mouse drugs rather than good human drugs' ".

Although the teachings of Bergers et al. (*Current Opinion in Genetics and Development.* 2000; **10**: 120-127) are drawn to specific antitumor agents, namely matrix metalloproteinase inhibitors, the great extent of unpredictability in the art is underscored by their disclosures. Bergers et al. teaches, "a body of data over the past few years indicate [...] that proteinases and proteinase inhibitors may, under special circumstance, either favor or block tumor progression. For

example, ectopic expression of TIMP-1 [a natural inhibitor of metalloproteinases] allows for some tumors to grow, while inhibiting others" (page 125, column 2). In fact, Bergers et al. discloses that the Bayer Corporation recently halted a clinical trial of a metalloproteinase inhibitor because patients given the drug experienced greater progression of cancer than did patients given a placebo (page 125, column 1). Bergers et al. comments, "these results are somewhat surprising and contrary to Bayers' preclinical data, which confirmed that the drug inhibited tumor activity in rodents" (page 124, columns 1-2). Bergers et al. also teaches that the absence of a metalloproteinase activity in mice actually predisposes the mice to *de novo* squamous carcinomas. Thus, the skilled artisan cannot accurately and reliably predict the effect of administering a pharmaceutical composition comprising an agent purported to have a desired pharmacological effect to a subject. Always the therapeutic effectiveness or efficacy of any unproven drug regimen can only be determined empirically. Therefore, it is submitted that if the specification is to be considered reasonably enabling of the claimed invention in such an unpredictable art as this, there should be working exemplification or the disclosure of the results of pre-clinical studies that are predictive of the outcome that will be achieved in its clinical application, which is reasonably commensurate in scope with the indicated uses of the claimed invention, as recited in the claims. Otherwise, the skilled artisan could not make and/or use the claimed invention without the need to first perform such undue experimentation.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

In deciding *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970), the Court indicated the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. "Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of

the public to understand and carry out the invention." *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1005 (CA FC 1997).

The specification does not teach the skilled artisan to use at least a substantial number of embodiments encompassed by the claims, nor does it teach the skilled artisan to make at least a substantial number of the "BMP-2 activity inhibitors" to which the claims are directed. The skilled artisan cannot predict whether any given embodiment can be used successfully to treat cancer; nor can the skilled artisan predict the structures of the "BMP-2 activity inhibitors" that are used in practicing the claimed invention. Rather, the skilled artisan can only identify embodiments of the claimed process that can be used to treat cancer by empirically testing the effectiveness of the process; and one cannot make or use the "BMP-2 activity inhibitors" without first determining which activities of BMP-2 can and should be inhibited to have the desired therapeutic effect and then designing and/or isolating and testing candidate "BMP-2 activity inhibitors" that are expected to cause such therapeutic effects. Therefore, amount and nature of the experimentation that would need be performed before the claimed invention could be used falls well into the realm of undue experimentation.

Thus, the overly broad scope of the claims would merely serve as an invitation to one skilled in the art to identify "BMP-2 activity inhibitors" that produce the desired therapeutic effect in a patient diagnosed with cancer; yet, defining a substance by its principal biological activity amounts to an alleged conception having no more specificity than that of a wish to know the identity of any material with that biological property. See *Colbert v. Lofdahl*, 21 USPQ2d 1068, 1071 (BPAI 1991).

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with *Ex parte Forman*, 230 USPQ 546 (BPAI 1986), the amount of guidance, direction, and exemplification contained in the supporting disclosure would not be sufficient to

enable the skilled artisan to use the claimed invention without undue experimentation.

Double Patenting

19. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

20. Claims 1 and 14-19 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 14 of copending Application No. 10/692,824. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons:

The instant claims are drawn to a method for the treatment of cancer comprising administering to a patient a therapeutically effective amount of a bone morphogenetic protein-2 (BMP-2) activity inhibitor, wherein said cancer is a carcinoma of the lung, the patient is human, and the BMP-2 activity inhibitor is

administered orally, enterically, intravenously, peritoneally, subcutaneously, transdermally, parenterally, intratumorally, or rectally.

Copending claims 1 and 14 are drawn to a method for reducing vascularization of a tumor in a subject comprising administering to a subject a therapeutically effective amount of a bone morphogenetic protein-2 (BMP-2) activity inhibitor. The portions of the specification of the copending application that best provide support for the claims and in particular the recitation of the term "tumor" indicate that the scope of the claimed invention includes a method for reducing the vascularization of a tumor in a subject, wherein said tumor is a carcinoma of the lung; see, e.g., page 1, paragraph [0004]; and page 5, paragraph [0015]. Although copending claim 1 recites the tumor in a "subject" is treated, given the therapeutic context of the claimed subject matter, it would have been obvious to regard the subject as a patient. At page 22, paragraph [068], the specification defines "patient" as preferably human. At page 32, paragraph [0091], the specification of the copending application defines the method of administration to specifically include orally, rectally, parenterally, enterically, subcutaneously, transdermally, peritoneally, intratumorally, or intravenously.

Accordingly, the claimed inventions are so substantially similar that for the most part, the claimed subject matter of the copending application anticipates the claimed subject matter of the instant application and any minor differences in the subject matter claimed in the instant application would be seen as an obvious variation of the subject matter claimed in the copending application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

21. No claim is allowed.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone

number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
April 15, 2005